RIBAVIRIN- ribavirin capsule
Sandoz Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RIBAVIRIN CAPSULES USP safely and effectively. See full prescribing information for RIBAVIRIN CAPSULES USP.
Ribavirin Capsules USP for oral use
Initial U.S. Approval: 1998

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

See full prescribing information for complete boxed warning.

Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C (5.10).
The hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin (2.4, 5.2).
Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy (4, 5.1, 8.1, 13.1, 17).

RECENT MAJOR CHANGES

Dose Modifications (2.4)	05/2013
Warnings and Precautions Impact on Growth – Pediatric Use (5.9)	11/2013

INDICATIONS AND USAGE

Ribavirin capsules USP are a nucleoside analogue indicated in combination with interferon alfa-2b for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age or older with compensated liver disease. (1.1)
Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

DOSAGE AND ADMINISTRATION

Ribavirin is administered according to body weight. (2.2)
Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal dysfunction (2.4, 2.5, 12.3)

DOSAGE FORMS AND STRENGTHS

Ribavirin 200 mg capsules (3)

CONTRAINDICATIONS

- Pregnant women and men whose female partners are pregnant (4, 8.1)
- Known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product (4)
- Autoimmune hepatitis (4)
- Hemoglobinopathies (4)
- Creatinine clearance less than 50 mL/min (4)
- Coadministration with didanosine (4, 7.1)

WARNINGS AND PRECAUTIONS

- ***Pregnancy Category X*** (5.1, 8.1, 8.3)
    - Birth defects and fetal death with ribavirin: Patients must have a negative pregnancy test prior to therapy; use at least 2 forms of contraception and undergo monthly pregnancy tests.

Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation

of therapy:

- Monotherapy with ribavirin is not permitted. (5.10)
- Hemolytic anemia may occur with a significant initial drop in hemoglobin. (5.2)
- Pancreatitis. (5.3)
- Pulmonary infiltrates or pulmonary function impairment. (5.4)
- New or worsening ophthalmologic disorders (5.5)
- Severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities. (5.6)
- Dental/periodontal disorders reported with combination therapy. (5.7)
- Weight loss and growth inhibition reported during combination therapy in pediatric patients. Long-term growth inhibition (height) reported in some patients. (5.9)

ADVERSE REACTIONS

Most common adverse reactions (approximately 40%) in adult patients receiving ribavirin/INTRON A combination therapy are injection site reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Nucleoside analogues: Closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin or both with worsening toxicities. (7.2)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Potential adverse reactions from the drug in nursing infants. (8.1, 8.3)
- Pediatrics: Safety and efficacy in patients less than 3 years old have not been established. (8.4)
- Organ transplant recipients: Safety and efficacy not studied. (8.6)
- Co-infected Patients: Safety and efficacy with HIV or HBV coinfection have not been established. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

- **Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. *[See Warnings and Precautions (5.10)]*.**
- **The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. *[See Dosage and Administration (2.4), and Warnings and Precautions (5.2)]*.**
- **Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period. *[See Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1), Nonclinical Toxicology (13.1), and Patient Counseling Information (17)]*.**

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis C (CHC)

Ribavirin capsules USP in combination with interferon alfa-2b (nonpegylated) are indicated for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age and older with compensated liver disease *[see Warnings and Precautions (5.9, 5.10), and Use in Specific Populations (8.4)]*.

The following points should be considered when initiating ribavirin combination therapy with INTRON A:

- These indications are based on achieving undetectable HCV-RNA after treatment for 24 or 48 weeks and maintaining a Sustained Virologic Response (SVR) 24 weeks after the last dose.
- Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection *[see Clinical Studies (14)]*.
- No safety and efficacy data are available for treatment of longer than one year.

2 DOSAGE AND ADMINISTRATION

Under no circumstances should ribavirin capsules be opened, crushed, or broken. Ribavirin should be taken with food *[see Clinical Pharmacology (12.3)]*. Ribavirin should not be used in patients with creatinine clearance less than 50 mL/min.

2.2 Ribavirin/INTRON A Combination Therapy

Adults

Duration of Treatment – Interferon Alpha-naïve Patients

The recommended dose of INTRON A is 3 million IU three times weekly subcutaneously. The recommended dose of ribavirin capsules depends on the patient's body weight (refer to **Table 1**). The recommended duration of treatment for patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen *[see Indications and Usage (1.1), and Clinical Studies (14)]*. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in the previously untreated patient population.

Duration of Treatment – Retreatment with INTRON A/Ribavirin in Relapse Patients

In patients who relapse following nonpegylated interferon monotherapy, the recommended duration of treatment is 24 weeks.

Table 1. Recommended Dosing

Body Weight	**Ribavirin Capsules**
≤75 kg	2 x 200 mg capsules AM 3 x 200 mg capsules PM daily orally
>75 kg	3 x 200 mg capsules AM 3 x 200 mg capsules PM daily orally

Pediatrics

The recommended dose of ribavirin is 15 mg/kg per day orally (divided dose AM and PM). INTRON A for Injection by body weight of 25 kg to 61 kg is 3 million IU/m^2 three times weekly subcutaneously.

The recommended duration of treatment is 48 weeks for pediatric patients with genotype 1. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by this time. The recommended duration of treatment for pediatric patients with genotype 2/3 is 24 weeks.

2.3 Laboratory Tests

The following laboratory tests are recommended for all patients treated with ribavirin, prior to beginning treatment and then periodically thereafter.

- Standard hematologic tests - including hemoglobin (pretreatment, Week 2 and Week 4 of therapy, and as clinically appropriate *[see Warnings and Precautions (5.2, 5.7)]*), complete and differential white blood cell counts, and platelet count.
- Blood chemistries - liver function tests and TSH.
- Pregnancy - including monthly monitoring for women of childbearing potential.
- ECG *[see Warnings and Precautions (5.2)]*.

2.4 Dose Modifications

If severe adverse reactions or laboratory abnormalities develop during combination ribavirin/INTRON A therapy modify, or discontinue the dose until the adverse reaction abates or decreases in severity *[see Warnings and Precautions (5)]*. If intolerance persists after dose adjustment, combination therapy should

be discontinued.

Ribavirin should not be used in patients with creatinine clearance less than 50 mL/min. Patients with impaired renal function and those over the age of 50 should be carefully monitored with respect to development of anemia *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5), and Clinical Pharmacology (12.3)]*.

Ribavirin should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped *[see Warnings and Precautions (5.2)]*.

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by greater than or equal to 2 g/dL during any 4-week period. In addition, for these cardiac history patients, if the hemoglobin remains less than 12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination therapy.

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her ribavirin dose modified or discontinued per **Table 2***[see Warnings and Precautions (5.2)]*.

Table 2. Guidelines for Dose Modification and Discontinuation of INTRON A Based on Laboratory Parameters in Adults and Pediatrics

Laboratory Parameters	**Reduce Ribavirin Daily Dose (see note 1) if:**	**Reduce INTRON A Dose (see note 2) if:**	**Discontinue Therapy if:**
WBC	N/A	1.0 to <1.5 x 10^9/L	<1.0 x 10^9/L
Neutrophils	N/A	0.5 to <0.75 x 10^9/L	<0.5 x 10^9/L
Platelets	N/A	25 to < 50 x 10^9/L (adults)	<25 x 10^9/L (adults)
	N/A	50 to <70 x 10^9/L (pediatrics)	<50 x 10^9/L (pediatrics)
Creatinine	N/A	N/A	>2 mg/dL (pediatrics)
Hemoglobin in patients without history of cardiac disease	8.5 to <10 g/dL	N/A	<8.5 g/dL
	Reduce Ribavirin Dose by 200 mg/day and INTRON A Dose by Half if:		
Hemoglobin in patients with history of stable cardiac disease*,†	≥2 g/dL decrease in hemoglobin during any four week period during treatment		<8.5 g/dL or <12 g/dL after four weeks of dose reduction

* Pediatric patients who have pre-existing cardiac conditions and experience a hemoglobin decrease greater than or equal to 2 g/dL during any 4-week period during treatment should have weekly evaluations and hematology testing.

† These guidelines are for patients with stable cardiac disease *[see Warnings and Precautions (5.2)]*.

Note 1: *Adult patients:* 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening. *Pediatric patients:* 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: *For patients on ribavirin/INTRON A combination therapy:* reduce INTRON A dose by 50%.

Refer to labeling for INTRON A for additional information about how to reduce an INTRON A dose.

2.5 Discontinuation of Dosing

Adults

Regardless of genotype, previously treated patients who have detectable HCV-RNA at week 12 or 24 are highly unlikely to achieve SVR and discontinuation of therapy should be considered.

3 DOSAGE FORMS AND STRENGTHS

Ribavirin 200 mg capsules

4 CONTRAINDICATIONS

Ribavirin combination therapy is contraindicated in:

- women who are pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. Ribavirin is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking ribavirin, the patient should be apprised of the potential hazard to her fetus *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1), and Patient Counseling Information (17)]*
- men whose female partners are pregnant
- patients with known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product
- patients with autoimmune hepatitis
- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- patients with creatinine clearance less than 50 mL/min. *[see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)]*
- Coadministration of ribavirin and didanosine is contraindicated because exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) is increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving didanosine in combination with ribavirin *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Pregnancy

Ribavirin capsules may cause birth defects and death of the unborn child. Ribavirin therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Patients should use at least two forms of contraception and have monthly pregnancy tests during treatment and during the 6-month period after treatment has been stopped. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin has demonstrated significant teratogenic and embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin. Ribavirin therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy *[see Boxed Warning, Contraindications (4), Use in Specific Populations (8.1), and Patient Counseling Information (17.2)]*.

5.2 Anemia

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of ribavirin/INTRON A-treated subjects in clinical trials. The anemia associated with ribavirin capsules occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained before the start of treatment and at week 2 and week 4 of therapy, or more frequently if clinically indicated. Patients should then be followed as clinically appropriate *[see Dosage and Administration (2.4, 2.5)]*.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued *[see Dosage and Administration (2.4, 2.5)]*. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin.

5.3 Pancreatitis

Ribavirin and INTRON A therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

5.4 Pulmonary Disorders

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia, have been reported during therapy with ribavirin with alpha interferon combination therapy; occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be closely monitored, and if appropriate, combination therapy should be discontinued.

5.5 Ophthalmologic Disorders

Ribavirin is used in combination therapy with alpha interferons. Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein, thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema, and serous retinal detachment are induced or aggravated by treatment with alpha interferons. All patients should receive an eye examination at baseline. Patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during combination therapy with alpha interferon treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Combination therapy with alpha interferons should be discontinued in patients who develop new or worsening ophthalmologic disorders.

5.6 Laboratory Tests

In the adult clinical trial, complete blood counts (including hemoglobin, neutrophil, and platelet counts) and chemistries (including AST, ALT, bilirubin, and uric acid) were measured during the treatment period at Weeks 2, 4, 8, 12, and then at 6-week intervals or more frequently if abnormalities developed. In pediatric subjects the same laboratory parameters were evaluated with additional assessment of hemoglobin at treatment Week 6. TSH levels were measured every 12 weeks during the treatment period. HCV-RNA should be measured periodically during treatment *[see Dosage and Administration (2)]*.

5.7 Dental and Periodontal Disorders

Dental and periodontal disorders have been reported in patients receiving ribavirin and interferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of ribavirin and interferon alfa-

2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. If vomiting occurs, they should be advised to rinse out their mouth thoroughly afterwards.

5.9 Impact on Growth - Pediatric Use

An impact on growth was seen in subjects after treatment with ribavirin and INTRON A combination therapy for one year. In a long-term follow-up trial of a limited number of these subjects, combination therapy resulted in reduced final adult height in some subjects *[see Adverse Reactions (6.2)]*.

5.10 Usage Safeguards

Based on results of clinical trials, ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, ribavirin capsules must not be used alone. The safety and efficacy of ribavirin capsules have only been established when used together with INTRON A (not other interferons) as combination therapy.

The safety and efficacy of ribavirin/INTRON A therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. Ribavirin capsules should not be used for these indications. Ribavirin for inhalation has separate labeling, which should be consulted if ribavirin inhalation therapy is being considered.

There are significant adverse reactions caused by ribavirin/INTRON A therapy, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up. Labeling for INTRON A should be reviewed in its entirety for additional safety information prior to initiation of combination treatment.

6 ADVERSE REACTIONS

Clinical trials with ribavirin in combination with INTRON A have been conducted in over 7800 subjects from 3 to 76 years of age.

The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1 to 2 weeks of oral therapy. Cardiac and pulmonary reactions associated with anemia occurred in approximately 10% of patients *[see Warnings and Precautions (5.2)]*.

Greater than 96% of all subjects in clinical trials experienced one or more adverse reactions. The most commonly reported adverse reactions in adult subjects receiving INTRON A in combination with ribavirin were injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. The most common adverse reactions in pediatric subjects, ages 3 and older, receiving ribavirin in combination with INTRON A were pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting.

The Adverse Reactions section references the following clinical trials:

- Ribavirin/INTRON A Combination Therapy trials for adults and pediatrics

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.2 Clinical Trials Experience - Ribavirin/INTRON A Combination Therapy

Adult Subjects

In clinical trials, 19% and 6% of previously untreated and relapse subjects, respectively, discontinued therapy due to adverse reactions in the combination arms compared to 13% and 3% in the interferon

arms. Selected treatment-related adverse reactions that occurred in the US trials with greater than or equal to 5% incidence are provided by treatment group (see **Table 3**). In general, the selected treatment-related adverse reactions were reported with lower incidence in the international trials as compared to the US trials with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

Pediatric Subjects

In clinical trials of 118 pediatric subjects 3 to 16 years of age, 6% discontinued therapy due to adverse reactions. Dose modifications were required in 30% of subjects, most commonly for anemia and neutropenia. In general, the adverse-reaction profile in the pediatric population was similar to that observed in adults. Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric subjects compared to adult subjects. Conversely, pediatric subjects experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritus compared to adult subjects. Selected treatment-related adverse reactions that occurred with greater than or equal to 5% incidence among all pediatric subjects who received the recommended dose of ribavirin/INTRON A combination therapy are provided in **Table 3**.

Table 3. Selected Treatment-Related Adverse Reactions: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects

	Percentage of Subjects						
	US Previously Untreated Study				US Relapse Study		Pediatric Subjects
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
Subjects Reporting Adverse Reactions*	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=231)	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=225)	INTRON A/ Ribavirin (N=77)	INTRON A/ Placebo (N=76)	INTRON A/ Ribavirin (N=118)
Application Site Disorders							
Injection site inflammation	13	10	12	14	6	8	14
Injection site reaction	7	9	8	9	5	3	19
Body as a Whole – General Disorders							
Headache	63	63	66	67	66	68	69
Fatigue	68	62	70	72	60	53	58
Rigors	40	32	42	39	43	37	25
Fever	37	35	41	40	32	36	61
Influenza-like symptoms	14	18	18	20	13	13	31
Asthenia	9	4	9	9	10	4	5
Chest pain	5	4	9	8	6	7	5
Central & Peripheral Nervous System Disorders							
Dizziness	17	15	23	19	26	21	20
Gastrointestinal System Disorders							
Nausea	38	35	46	33	47	33	33
Anorexia	27	16	25	19	21	14	51
Dyspepsia	14	6	16	9	16	9	<1
Vomiting	11	10	9	13	12	8	42

Musculoskeletal System Disorders							
Myalgia	61	57	64	63	61	58	32
Arthralgia	30	27	33	36	29	29	15
Musculoskeletal pain	20	26	28	32	22	28	21
Psychiatric Disorders							
Insomnia	39	27	39	30	26	25	14
Irritability	23	19	32	27	25	20	10
Depression	32	25	36	37	23	14	13
Emotional lability	7	6	11	8	12	8	16
Concentration impaired	11	14	14	14	10	12	5
Nervousness	4	2	4	4	5	4	3
Respiratory System Disorders							
Dyspnea	19	9	18	10	17	12	5
Sinusitis	9	7	10	14	12	7	<1
Skin and Appendages Disorders							
Alopecia	28	27	32	28	27	26	23
Rash	20	9	28	8	21	5	17
Pruritus	21	9	19	8	13	4	12
Special Senses, Other Disorders							
Taste perversion	7	4	8	4	6	5	<1

* Subjects reporting one or more adverse reactions. A subject may have reported more than one adverse reaction within a body system/organ class category.

During a 48-week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 7%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 9%). A general reversal of these trends was noted during the 24-week post-treatment period. Long-term data in a limited number of patients, however, suggests that combination therapy may induce a growth inhibition that results in reduced final adult height in some patients *[see Warnings and Precautions (5.9)]*.

Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **Table 4**).

Hemoglobin

Hemoglobin decreases among subjects receiving ribavirin therapy began at Week 1, with stabilization by Week 4. In previously untreated subjects treated for 48 weeks, the mean maximum decrease from baseline was 3.1 g/dL in the US trial and 2.9 g/dL in the international trial. In relapse subjects the mean maximum decrease from baseline was 2.8 g/dL in the US trial and 2.6 g/dL in the international trial. Hemoglobin values returned to pretreatment levels within 4 to 8 weeks of cessation of therapy in most subjects.

Bilirubin and Uric Acid

Increases in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most were moderate biochemical changes and were reversed within 4 weeks after treatment discontinuation. This observation occurred most frequently in subjects with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

Table 4. Selected Laboratory Abnormalities During Treatment with Ribavirin Capsules and INTRON A: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects

	Percentage of Subjects						
	US Previously Untreated Study				US Relapse Study		Pediatric Subjects
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=231)	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=225)	INTRON A/ Ribavirin (N=77)	INTRON A/ Placebo (N=76)	INTRON A/ Ribavirin (N=118)
Hemoglobin (g/dL)							
9.5 to 10.9	24	1	32	1	21	3	24
8.0 to 9.4	5	0	4	0	4	0	3
6.5 to 7.9	0	0	0	0.4	0	0	0
<6.5	0	0	0	0	0	0	0
Leukocytes ($x10^9$/L)							
2.0 to 2.9	40	20	38	23	45	26	35
1.5 to 1.9	4	1	9	2	5	3	8
1.0 to 1.4	0.9	0	2	0	0	0	0
<1.0	0	0	0	0	0	0	0
Neutrophils ($x10^9$/L)							
1.0 to 1.49	30	32	31	44	42	34	37
0.75 to 0.99	14	15	14	11	16	18	15
0.5 to 0.74	9	9	14	7	8	4	16
<0.5	11	8	11	5	5	8	3
Platelets ($x10^9$/L)							
70 to 99	9	11	11	14	6	12	0.8
50 to 69	2	3	2	3	0	5	2
30 to 49	0	0.4	0	0.4	0	0	0
<30	0.9	0	1	0.9	0	0	0
Total Bilirubin (mg/dL)							
1.5 to 3.0	27	13	32	13	21	7	2
3.1 to 6.0	0.9	0.4	2	0	3	0	0
6.1 to 12.0	0	0	0.4	0	0	0	0
>12.0	0	0	0	0	0	0	0

6.3 Postmarketing Experiences

The following adverse reactions have been identified and reported during post approval use of ribavirin in combination with INTRON A. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System disorders

Pure red cell aplasia, aplastic anemia

Ear and Labyrinth disorders

Hearing disorder, vertigo

Respiratory, Thoracic and Mediastinal disorders

Pulmonary hypertension

Eye disorders

Serous retinal detachment

Endocrine disorders

Diabetes

7 DRUG INTERACTIONS

7.1 Didanosine

Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin, which could cause or worsen clinical toxicities; therefore, coadministration of ribavirin capsules and didanosine is contraindicated. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials.

7.2 Nucleoside Analogues

Hepatic decompensation (some fatal) has occurred in cirrhotic HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alpha and ribavirin. Adding treatment with alpha interferons alone or in combination with ribavirin may increase the risk in this patient population. Patients receiving interferon with ribavirin and nucleoside reverse transcriptase inhibitors (NRTIs) should be closely monitored for treatment-associated toxicities, especially hepatic decompensation and anemia. Discontinuation of NRTIs should be considered as medically appropriate *[see labeling for individual NRTI product]*. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

Ribavirin may antagonize the *cell culture* antiviral activity of stavudine and zidovudine against HIV. Ribavirin has been shown in cell culture to inhibit phosphorylation of lamivudine, stavudine and zidovudine, which could lead to decreased antiretroviral activity. Therefore, concomitant use of ribavirin with either of these drugs should be used with caution.

7.3 Drugs Metabolized by Cytochrome P-450

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P450 enzyme-mediated metabolism of ribavirin, with minimal potential for P450 enzyme-based drug interactions.

No pharmacokinetic interactions were noted between INTRON A and ribavirin capsules in a multiple-dose pharmacokinetic study.

7.4 Azathioprine

The use of ribavirin for the treatment of chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioinosine monophosphate (6-MTITP), which is associated with myelotoxicity

(neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

[See Contraindications (4), Warnings and Precautions (5.1), and Nonclinical Toxicology (13.1)].

Treatment and Posttreatment

Potential Risk to the Fetus

Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 to 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 times the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

Women of childbearing potential should not receive ribavirin unless they are using effective contraception (two reliable forms) during the therapy period. In addition, effective contraception should be utilized for 6 months post-therapy based on a multiple-dose half-life (t1/2) of ribavirin of 12 days.

Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with ribavirin and for the 6-month post-therapy period (e.g., 15 half-lives for ribavirin clearance from the body).

A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

8.3 Nursing Mothers

It is not known whether the ribavirin product is excreted in human milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue ribavirin capsules.

8.4 Pediatric Use

For treatment with ribavirin/INTRON A, evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety findings observed.

Long-term follow-up data in pediatric subjects indicates that ribavirin in combination with INTRON A may induce a growth inhibition that results in reduced height in some patients *[see Warnings and Precautions (5.9) and Adverse Reactions (6.2)]*.

Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% vs. 1%) during treatment and off-therapy follow-

up *[see Warnings and Precautions (5.10)]*. As in adult patients, pediatric patients experienced other psychiatric adverse reactions (e.g., depression, emotional lability, somnolence), anemia, and neutropenia *[see Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Clinical trials of ribavirin/INTRON A therapy did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects.

Ribavirin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments should be made accordingly. Ribavirin should not be used in patients with creatinine clearance less than 50 mL/min *[see Contraindications (4)]*.

In general, ribavirin capsules should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and cardiac function, and of concomitant disease or other drug therapy. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than younger patients (28%) *[see Warnings and Precautions (5.2)]*.

8.6 Organ Transplant Recipients

The safety and efficacy of INTRON A alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been established. In a small (n=16) single-center, uncontrolled case experience, renal failure in renal allograft recipients receiving interferon alpha and ribavirin combination therapy was more frequent than expected from the center's previous experience with renal allograft recipients not receiving combination therapy. The relationship of the renal failure to renal allograft rejection is not clear.

8.7 HIV or HBV Co-infection

The safety and efficacy of INTRON A/ribavirin for the treatment of patients with HCV co-infected with HIV or HBV have not been established.

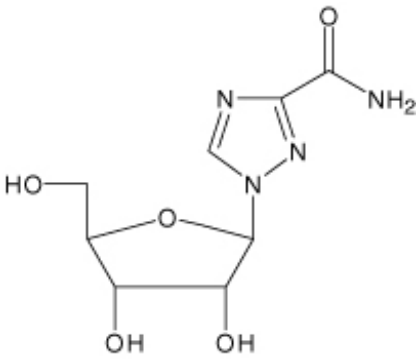
10 OVERDOSAGE

There is limited experience with overdosage. Acute ingestion of up to 20 g of ribavirin capsules, INTRON A ingestion of up to 120 million units, and subcutaneous doses of INTRON A up to 10 times the recommended doses have been reported. Primary effects that have been observed are increased incidence and severity of the adverse reactions related to the therapeutic use of INTRON A and ribavirin. However, hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with administration of single subcutaneous doses of INTRON A that exceed dosing recommendations.

There is no specific antidote for INTRON A or ribavirin overdose, and hemodialysis and peritoneal dialysis are not effective for treatment of overdose of these agents.

11 DESCRIPTION

Ribavirin is a synthetic nucleoside analogue (purine analogue). The chemical name of ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

Ribavirin capsules USP consist of a white powder in a white, opaque, gelatin capsule. Each capsule, for oral administration, contains 200 mg ribavirin. In addition, each capsule contains the following inactive ingredients: corn starch, croscarmellose sodium, hypromellose, magnesium stearate, mannitol and povidone. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of FD&C Blue #2 aluminum lake, propylene glycol, shellac and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ribavirin is an antiviral agent *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Single- and multiple-dose pharmacokinetic properties in adults are summarized in **Table 5**. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and AUC_{tf} (AUC from time zero to last measurable concentration) following single doses of 200 to 1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400 to 600 mg.

Upon multiple oral dosing, based on $AUC12_{hr}$, a 6 fold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg twice daily, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 ng/mL (37%). Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

Effect of Antacid on Absorption of Ribavirin

Coadministration of ribavirin capsules with an antacid containing magnesium, aluminum, and simethicone resulted in a 14% decrease in mean ribavirin AUCtf. The clinical relevance of results from this single-dose study is unknown.

Table 5. Mean (% CV) Pharmacokinetic Parameters for Ribavirin Capsules When Administered Individually to Adults

Parameter	Ribavirin Capsules	
	Single-Dose 600 mg Capsules	**Multiple-Dose 600 mg Capsules twice daily**

	(N=12)	(N=12)
T_{max} (hr)	1.7 (46)*	3 (60)
C_{max} (ng/mL)	782 (37)	3680 (85)
AUC_{tf} (ng hr/mL)	13400 (48)	228000 (25)
$T_{1/2}$ (hr)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)	2825 (9)†	
Apparent Clearance (L/hr)	38.2 (40)	
Absolute Bioavailability	64% (44)‡	

* N=11

† Data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N=5

‡ N=6

Tissue Distribution

Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells, and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the extensive volume of distribution. Ribavirin does not bind to plasma proteins.

Metabolism and Excretion

Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

Special Populations

Renal Dysfunction

The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to non HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance greater than 90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC_{tf} was twofold greater when compared to control subjects. The increased AUC_{tf} appears to be due to reduction of renal and nonrenal clearance in these subjects. Phase 3 efficacy trials included subjects with creatinine clearance values greater than 50 mL/min. The multiple-dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance less than 50 mL/min should not be treated with ribavirin *[see Contraindications (4)]*.

Hepatic Dysfunction

The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC_{tf} values were not significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.

Elderly Patients

Pharmacokinetic evaluations in elderly subjects have not been performed.

Pediatric Patients

Multiple-dose pharmacokinetic properties for ribavirin capsules and INTRON A in pediatric subjects with chronic hepatitis C between 5 and 16 years of age are summarized in **Table 6.** The pharmacokinetics of ribavirin and INTRON A (dose-normalized) are similar in adults and pediatric subjects.

Complete pharmacokinetic characteristics of ribavirin oral solution have not been determined in pediatric subjects. Ribavirin C_{min} values were similar following administration of ribavirin oral solution or ribavirin capsules during 48 weeks of therapy in pediatric subjects (3 to 16 years of age).

Table 6: Mean (% CV) Multiple-dose Pharmacokinetic Parameters for INTRON A and Ribavirin Capsules When Administered to Pediatric Subjects with Chronic Hepatitis C

Parameter	**Ribavirin 15 mg/kg/day as 2 divided doses (N=17)**	**INTRON A 3 MIU/m^2 three times weekly (N=54)**
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3275 (25)	51 (48)
AUC*	29774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	ND†

Note: numbers in parenthesis indicate % coefficient of variation.

* AUC_{12} (ng·hr/mL) for Ribavirin; AUC_{0-24} (IU•hr/mL) for INTRON A

† ND=not done

Effect of Food on Absorption of Ribavirin

Both AUC_{tf} and C_{max} increased by 70% when ribavirin capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study *[see Dosage and Administration (2)]*.

12.4 Microbiology

Mechanism of Action

The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. Ribavirin has direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

Antiviral Activity in Cell Culture

The anti-viral activity of ribavirin in the HCV-replicon is not well understood and has not been defined because of the cellular toxicity of ribavirin. Direct anti-viral activity has been observed in tissue culture of other RNA viruses. The anti-HCV activity of interferon was demonstrated in cell containing self-replicating HCV-RNS (HCV replicon cells) or HCV infection.

Cross-resistance

There is no reported cross-resistance between non-pegylated interferons and ribavirin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was noncarcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult).

Mutagenesis

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20 to 200 mg/kg (estimated human equivalent of 1.67 to 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 to 1 times the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Impairment of Fertility

Ribavirin demonstrated significant embryocidal and teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no-effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 times the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 times the maximum recommended human 24-hour dose of ribavirin) *[see Contraindications (4), and Warnings and Precautions (5.1)]*.

Fertile women and partners of fertile women should not receive ribavirin unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple-dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months post-therapy (e.g., 15 half-lives of clearance for ribavirin).

Ribavirin should be used with caution in fertile men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 to 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 to 0.8 times the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

13.2 Animal Toxicology and Pharmacology

Long-term studies in the mouse and rat [18 to 24 months; doses of 20 to 75 and 10 to 40 mg/kg/day, respectively [estimated human equivalent doses of 1.67 to 6.25 and 1.43 to 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 to 0.4 times the maximum human 24-hour dose of ribavirin] have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin treated rats.

In a study in which rat pups were dosed postnatally with ribavirin at doses of 10, 25, and 50 mg/kg/day, drug-related deaths occurred at 50 mg/kg (at rat pup plasma concentrations below human plasma concentrations at the human therapeutic dose) between study Days 13 and 48. Rat pups dosed from postnatal Days 7 through 63 demonstrated a minor, dose-related decrease in overall growth at all doses, which was subsequently manifested as slight decreases in body weight, crown-rump length, and bone length. These effects showed evidence of reversibility, and no histopathological effects on bone were observed. No ribavirin effects were observed regarding neurobehavioral or reproductive development.

14 CLINICAL STUDIES

14.2 Ribavirin/INTRON A Combination Therapy

Adult Subjects

Previously Untreated Subjects

Adults with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) who were previously untreated with alpha interferon therapy were enrolled into two multicenter, double-blind trials (US and international) and randomized to receive ribavirin capsules 1200 mg/day (1000 mg/day for subjects weighing less than or equal to 75 kg) and INTRON A 3 MIU three times weekly or INTRON A and placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The international trial did not contain a 24-week INTRON A and placebo treatment arm. The US trial enrolled 912 subjects who, at baseline, were 67% male, 89% Caucasian with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The international trial, conducted in Europe, Israel, Canada, and Australia, enrolled 799 subjects (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Trial results are summarized in **Table 7**.

Table 7. Virologic and Histologic Responses: Previously Untreated Subjects*

	US Trial				International Trial		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=231)	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=225)	INTRON A/ Ribavirin (N=265)	INTRON A/ Ribavirin (N=268)	INTRON A/ Placebo (N=266)
Virologic Response							
Responder†	65 (29)	13 (6)	85 (37)	27 (12)	86 (32)	113 (42)	46 (17)
Nonresponder	147 (64)	194 (84)	110 (48)	168 (75)	158 (60)	120 (45)	196 (74)
Missing Data	16 (7)	24 (10)	33 (14)	30 (13)	21 (8)	35 (13)	24 (9)
Histologic Response							
Improvement‡	102 (45)	77 (33)	96 (42)	65 (29)	103 (39)	102 (38)	69 (26)
No improvement	77 (34)	99 (43)	61 (27)	93 (41)	85 (32)	58 (22)	111 (41)
Missing Data	49 (21)	55 (24)	71 (31)	67 (30)	77 (29)	108 (40)	86 (32)

* Number (%) of subjects.

† Defined as HCV RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.

‡ Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III)

improvement of greater than or equal to 2 points.

Of subjects who had not achieved HCV-RNA below the limit of detection of the research-based assay by Week 24 of ribavirin/INTRON A treatment, less than 5% responded to an additional 24 weeks of combination treatment.

Among subjects with HCV Genotype 1 treated with ribavirin/INTRON A therapy who achieved HCV-RNA below the detection limit of the research-based assay by 24 weeks, those randomized to 48 weeks of treatment had higher virologic responses compared to those in the 24-week treatment group. There was no observed increase in response rates for subjects with HCV nongenotype 1 randomized to ribavirin/INTRON A therapy for 48 weeks compared to 24 weeks.

Relapse Subjects

Subjects with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (US and international) and randomized to receive ribavirin 1200 mg/day (1000 mg/day for subjects weighing ≤75 kg) and INTRON A 3 MIU three times weekly or INTRON A and placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The US trial enrolled 153 subjects who, at baseline, were 67% male, 92% Caucasian with a mean Knodell HAI score (I+II+III) of 6.8, and 58% genotype 1. The international trial, conducted in Europe, Israel, Canada, and Australia, enrolled 192 subjects (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1). Trial results are summarized in **Table 8.**

Table 8. Virologic and Histologic Responses: Relapse Subjects*

	US Trial		International Trial	
	INTRON A/ Ribavirin (N=77)	**INTRON A/ Placebo (N=76)**	**INTRON A/ Ribavirin (N=96)**	**INTRON A/ Placebo (N=96)**
Virologic Response				
Responder†	33 (43)	3 (4)	46 (48)	5 (5)
Nonresponder	36 (47)	66 (87)	45 (47)	91 (95)
Missing Data	8 (10)	7 (9)	5 (5)	0 (0)
Histologic Response				
Improvement‡	38 (49)	27 (36)	49 (51)	30 (31)
No improvement	23 (30)	37 (49)	29 (30)	44 (46)
Missing Data	16 (21)	12 (16)	18 (19)	22 (23)

* Number (%) of subjects.

† Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.

‡ Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of greater than or equal to 2 points.

Virologic and histologic responses were similar among male and female subjects in both the previously untreated and relapse trials.

Pediatric Subjects

Pediatric subjects 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were treated with ribavirin 15 mg/kg per day and INTRON A 3 MIU/m^2 three times weekly for 48 weeks followed by 24 weeks of off-therapy follow-up. A total of 118 subjects received treatment of which 57% were male, 80%

Caucasian, and 78% genotype 1. Subjects less than 5 years of age received ribavirin oral solution and those 5 years of age or older received either ribavirin oral solution or capsules.

Trial results are summarized in **Table 9**.

Table 9: Virologic Response: Previously Untreated Pediatric Subjects*

	INTRON A 3 MIU/m^2 three times weekly/ Ribavirin 15 mg/kg/day
Overall Response† (N=118)	54 (46)
Genotype 1 (N=92)	33 (36)
Genotype non-1 (N=26)	21 (81)

* Number (%) of subjects.

† Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to INTRON A/ ribavirin combination therapy compared to subjects with genotype non-1, 36% vs. 81%. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 26% (13/50).

16 HOW SUPPLIED/STORAGE AND HANDLING

Ribavirin capsules USP, 200 mg are white, opaque, hard gelatin capsules imprinted (in blue) RIBAVIRIN over 200 mg on cap and GG 608 on body, and are supplied as follows:

NDC 0781-2043-42 in bottles of 42 capsules
NDC 0781-2043-16 in bottles of 56 capsules
NDC 0781-2043-67 in bottles of 70 capsules
NDC 0781-2043-04 in bottles of 84 capsules
NDC 0781-2043-01 in bottles of 100 capsules
NDC 0781-2043-28 in bottles of 168 capsules
NDC 0781-2043-10 in bottles of 1000 capsules

Dispense in a tight container as defined in the USP.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]

INTRON® A is a registered trademark of Schering Corporation.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved Patient Labeling (Medication Guide).

Anemia

The most common adverse experience occurring with ribavirin capsules is anemia, which may be severe *[see Warnings and Precautions (5.2) and ADVERSE REACTIONS (6)]*. Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter *[see Dosage and Administration (2.3)]*. It is advised that patients be well hydrated, especially during the initial stages of treatment.

Pregnancy

Patients must be informed that ribavirin capsules may cause birth defects and death of the unborn child. Ribavirin must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking ribavirin. Ribavirin should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months post therapy. Women of childbearing potential must be counseled about use of effective contraception (two reliable forms) prior to initiating therapy. Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during ribavirin and for 6 months post therapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1)]*.

If pregnancy does occur during treatment or during 6 months post therapy, the patient must be advised of the teratogenic risk of ribavirin therapy to the fetus. Patients, or partners of patients, should immediately report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician. Prescribers should report such cases by calling 1-800-593-2214.

Risks versus Benefits

Patients receiving ribavirin capsules should be informed of the benefits and risks associated with treatment, directed in its appropriate use, and referred to the patient **MEDICATION GUIDE**. Patients should be informed that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus should be taken.

Patients should be informed about what to do in the event they miss a dose of ribavirin; the missed dose should be taken as soon as possible during the same day. Patients should not double the next dose. Patients should be advised to contact their healthcare provider if they have questions.

MEDICATION GUIDE

Ribavirin Capsules USP 200 mg

(rye-bah-VYE-rin)

Read this Medication Guide before you start taking ribavirin, and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about ribavirin?

1. **Do Not take ribavirin alone to treat chronic hepatitis C infection**. Ribavirin should be used in combination with **interferon alfa-2b (Intron A)** to treat chronic hepatitis C infection.
2. **Ribavirin may cause a significant drop in your red blood cell count and cause anemia in some cases. Anemia has been associated with worsening of Heart Problems and in rare cases can cause a Heart Attack and Death.** Tell your healthcare provider if you have ever had any heart problems. Ribavirin may not be right for you. **Seek medical attention right away if you experience chest pain.**
3. **Ribavirin may cause Birth Defects or the Death of your unborn baby. Do Not Take Ribavirin if you or your sexual partner is pregnant, or plan to become pregnant. Do Not become Pregnant within 6 months after discontinuing ribavirin therapy.** You must use 2 forms of birth control when you take ribavirin and for the 6 months after treatment.

    - Females must have a pregnancy test before starting ribavirin, every month while taking ribavirin, and every month for the 6 months after the last dose of ribavirin.
    - **If you or your female sexual partner becomes pregnant while taking ribavirin or within 6 months after you stop taking ribavirin, tell your healthcare provider right away. You**

or your healthcare provider should contact the ribavirin pregnancy registry by calling 1-800-593-2214. The ribavirin pregnancy registry collects information about what happens to mothers and their babies if the mother takes ribavirin while she is pregnant.

What is ribavirin?

Ribavirin is a medicine used with interferon alfa-2b (Intron A) to treat chronic (lasting a long time) hepatitis C infection in people 3 years and older with liver disease.

It is not known if ribavirin use for longer than one year is safe and will work.

It is not known if ribavirin use in children younger than 3 years old is safe and will work.

Who should not take ribavirin?

See "What is the most important information I should know about ribavirin?"

Do not take ribavirin if you have:

- or ever had serious allergic reactions to the ingredients in ribavirin capsules. See the end of this Medication Guide for a complete list of ingredients.
- certain types of hepatitis (autoimmune hepatitis).
- certain blood disorders (hemoglobinopathies).
- severe kidney disease.
- taken or currently take didanosine (VIDEX®).

Talk to your healthcare provider before taking ribavirin if you have any of these conditions.

What should I tell my healthcare provider before taking ribavirin?

Before you take ribavirin, tell your healthcare provider if you have or ever had:

- treatment for hepatitis C that did not work for you.
- breathing problems. ribavirin may cause or worsen breathing problems you already have.
- vision problems. Ribavirin may cause eye problems or worsen eye problems you already have. You should have an eye exam before you start treatment with ribavirin.
- certain blood disorders such as anemia (low red blood cell count).
- high blood pressure, heart problems, or have had a heart attack. Your healthcare provider should check your blood and heart before you start treatment with ribavirin.
- thyroid problems
- liver problems other than hepatitis C infection
- human immunodeficiency virus (HIV) or any immunity problems
- mental health problems, including depression or thoughts of suicide
- kidney problems
- an organ transplant
- diabetes. Ribavirin may make your diabetes worse or harder to treat.
- any other medical condition
- are breastfeeding. It is not known if ribavirin passes into your breast milk. You and your healthcare provider should decide if you will take ribavirin or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription medicines, vitamins, and herbal supplements. Ribavirin may affect the way other medicines work.

Especially tell your healthcare provider if you take didanosine (VIDEX®) or azathioprine

(Imuran® and Azasan®).

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take ribavirin?

- Take ribavirin exactly as your healthcare provider tells you. Your healthcare provider will tell you how much ribavirin to take and when to take it.
- Take ribavirin with food.
- Take **ribavirin capsules** whole. Do not open, break, or crush **ribavirin capsules** before swallowing. If you cannot swallow **ribavirin capsules** whole, tell your healthcare provider.
- If you miss a dose of ribavirin, take the missed dose as soon as possible during the same day. Do not double the next dose. If you have questions about what to do, call your healthcare provider.
- If you take too much ribavirin, call your healthcare provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of ribavirin?

Ribavirin may cause serious side effects, including: See "What is the most important information I should know about ribavirin?"

- **Swelling and irritation of your pancreas (pancreatitis).** You may have stomach pain, nausea, vomiting, or diarrhea.
- **Serious breathing problems.** Difficulty breathing may be a sign of a serious lung infection (pneumonia) that can lead to death.
- **Serious eye problems** that may lead to vision loss or blindness.
- **Dental problems.** Your mouth may be very dry, which can lead to problems with your teeth and gums.
- **Severe depression**
- **Suicidal thoughts and attempts.** Adults and children who take ribavirin, especially teenagers are more likely to have suicidal thoughts or attempt to hurt themselves while taking ribavirin. Call your healthcare provider right away or go to the nearest hospital emergency room if you have new or worse depression or thoughts about suicide or dying.
- **Severe blood disorders.** An increased risk when used in combination with azathioprine
- **Growth problems in children.** Weight loss and slowed growth are common in children during combination treatment with INTRON A. Most children will go through a growth spurt and gain weight after treatment stops. Some children may not reach the height that they were expected to have before treatment. Talk to your healthcare provider if you are concerned about your child's growth during treatment with ribavirin and INTRON A.

Tell your healthcare provider right away if you have any side effect that bothers you or that does not go away.

The most common side effects of ribavirin include:

- flu-like symptoms - feeling tired, headache, shaking along with high temperature (fever), nausea, and muscle aches.
- mood changes, feeling irritable.

The most common side effects of ribavirin in children include:

- a decrease in the blood cells that fight infection (neutropenia).

- a decrease in appetite.
- stomach pain and vomiting.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ribavirin. For more information ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ribavirin?

- Store **ribavirin capsules** between 59°F to 86°F (15°C to 30°C).

Keep ribavirin and all medicines out of the reach of children.

GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF RIBAVIRIN.

It is not known if treatment with ribavirin will cure hepatitis C virus infections or prevent cirrhosis, liver failure, or liver cancer that can be caused by hepatitis C virus infections. It is not known if taking ribavirin will prevent you from infecting another person with the hepatitis C virus.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ribavirin for a condition for which it was not prescribed. Do not give ribavirin to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about ribavirin. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or health care provider for information about ribavirin that is written for health professionals.

What are the ingredients in ribavirin capsules USP?

Active ingredient: ribavirin

Inactive ingredients: corn starch, croscarmellose sodium, hypromellose, magnesium stearate, mannitol, and povidone. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of FD&C Blue #2 aluminum lake, propylene glycol, shellac and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

INTRON® A is a registered trademark of Schering Corporation.

VIDEX® is a registered trademark of Bristol-Myers Squibb Company.

Imuran ® is a registered trademark of Prometheus Laboratories, Inc.

Azasan ® is a registered trademark of AAI Pharma, Inc.

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Sandoz Inc.

Princeton, NJ 08540

200 mg Label

NDC 0781-2043-42

Ribavirin

Capsules

USP 200 mg

For combination use with INTRON® A

(Interferon alfa-2b, recombinant) Injection*

42 Capsules Rx only

*INTRON® A is a registered

trademark of Schering Corporation.

SANDOZ

RIBAVIRIN

ribavirin capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0781-2043
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
RIBAVIRIN (RIBAVIRIN)	RIBAVIRIN	200 mg

Inactive Ingredients	
Ingredient Name	**Strength**
STARCH, CORN	
CROSCARMELLOSE SODIUM	
FD&C BLUE NO. 2	
GELATIN	
HYPROMELLOSE 2910 (6 MPA.S)	
MAGNESIUM STEARATE	
MANNITOL	
POVIDONES	

PROPYLENE GLYCOL	
SHELLAC	
TITANIUM DIOXIDE	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	RIBAVIRIN200mg;GG608
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-2043-42	42 in 1 BOTTLE		
2	NDC:0781-2043-16	56 in 1 BOTTLE		
3	NDC:0781-2043-67	70 in 1 BOTTLE		
4	NDC:0781-2043-04	84 in 1 BOTTLE		
5	NDC:0781-2043-01	100 in 1 BOTTLE		
6	NDC:0781-2043-28	168 in 1 BOTTLE		
7	NDC:0781-2043-10	1000 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076192	04/06/2004	

Labeler - Sandoz Inc (110342024)

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